

III. REMARKS

Claims 13-18, 40, 41, and 44-46 are pending. Claims 13, 17, 18, 40, 41, and 45 have been amended. Claims 44 and 46 have been cancelled without prejudice. Claim 47 has been newly added to replace rejected claim 44 in amended and clean form. The amendment is supported by the disclosure and does not introduce new matter. The number of presently pending claims does not exceed the number of rejected claims.

Examiner's Position:

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

Claim 46 is rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter, "the computer-controlled method for rare cell image identification, wherein the x-y-coordinates are a planar coordination component.. ."

In the opinion of the Examiner, the method step of claim 46 neither results in a physical transformation of matter, nor produces a result that is concrete, tangible and useful, as required by 35 USC § 101. The method does not result in a physical transformation of matter.

Applicant's response:

Applicant respectfully traverses the rejection since by clerical error the claim was not shown as dependent from claim 44 as intended. Claim 46 has been cancelled without prejudice.

The rejection is deemed moot.

Claim Rejections -35 USC § 112-New Matter

Claims 13-18, 40, 41, and 44-46 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges the following: that independent claim 44 recites new matter in step (iii) of “precisely locating a rare cell candidate in said blob and continuously recording x, y, and z-coordinates thereof with a computer controlled mobile microscope system searching said optical field starting from an initial position on an optical field of said monolayer”, that the specification allegedly provides for “recording a physical location” via a “computer controlled x-y mechanical stage” in which “the image provided by the camera is digitized” (page 12, lines 5-8; lines 22-28), a motorized X-Y stage at page 21, lines 1-9, and at page 23, and that the specification discloses that the x-y position of the stage at the starting point is recorded (line 9) and the z-y position is stored in a database (lines 27 and 28),. In the opinion of the Examiner, the specification allegedly fails to disclose the limitation present in instant step (iii) of claim 44 and therefore is deemed new matter.

The Examiner also contends that Applicant has not provided support for base Claim 44, and dependent claims 14, and 15 when reciting “enhancing detection of said rare cell color image by applying different computer implemented HLS signal masks with selectively limiting pixel value.” Further, the Examiner objects to the Claim 44 phrase of “automatically locating by a selective tag dispensing system” because Applicant has allegedly not provided support for such a

limitation nor is support apparent in the instant specification or claims as originally filed.

According to the Examiner, the specification discloses a “device for dispensing reagents” on page 28, but no disclosure of a “selective” tag dispensing system.

The Examiner further objects to Claim 44, as reciting the broad step of “isolating” a sample. In his opinion, receiving a sample and creating a smear are not support for the full scope of “isolating” a sample.

Applicant's response:

Applicant respectfully traverses the Examiner's reasons for the rejection. In the first instance, taking reference to the instant published application US2002/0160443, the claimed invention as presently amended in new claim 47, replacing cancelled claim 44, is directed to an *automated* process, see paragraph [0057], wherein the rare cell identification is computer-implemented according to certain appropriately *programmed* steps in order to generate rapidly a large number of data from a large sample deposited on a multiplicity of substrates. As claimed, the automated step are (i) preparing a sample comprising cells from a body fluid or tissue, (ii) depositing, fixing and optionally staining said cell sample in a monolayer on a substrate, comprising rare cells or blobs containing rare cells, see paragraph [0010], (iii) scanning and digitizing said monolayer by starting from an origin (x_1, y_1) continuously digitally recording and computer memory storing x and y coordinates as well as focal y-z coordinates thereof, see paragraph [0070], (iv) digitally receiving a native (*i.e.*, unstained) or stained color image of a rare cell candidate or a blob containing a rare cell candidate, (v) transforming the digital color image signal

to a binary quantized processing color space represented by Hue, Luminescence and Saturation (HLS); (vi) enhancing detection of said rare cell color image by applying a computer implemented HLS signal mask with limiting pixel values; (vii) identifying said rare cell candidate by automatically measuring pre-set criteria of the digitized image of a cell or cell nucleus, in terms of size, morphology, and characteristic cell markers; and(viii) automatically locating a computer controlled label dispensing system over said rare cell, which system is programmed to tag selectively said rare cell *in situ* to determine biological criteria comprising genomic variation, mutation, or chromosomal abnormality, as described in Fig. 7 and paragraph [0194] and [0195]. Contrary to the Examiner's contention, the Specification describes a reagent dispenser having a narrow tip adjacent to the stage with *more than one* feed line extending through suitable pumps to reagent containers for delivery of different reagents from reagent container to reagent dispenser. One of ordinary skill would know to use selective tagging reagents given the availability of more than one reagent container. Moreover, the system is automatic given the fact that the pumps are electronically controlled by computer using specifically compiled software commands indicated by "reagent control". The reagents can be any one of the reagents described above in connection with generating a signal. Finally, Applicant respectfully asserts that the precision of locating and revisiting of certain optical field coordinates is inherently and by necessity precise and repeatable thereby affording a completely automated and computerized analysis, including the monolayer rare cell specimen preparation chapter 6.2 of the instant specification. Applicant requests removal of the "new matter" rejection under the above-referenced statute.

Claim Rejections -35 USC § 112-Enablement

The Examiner's Position:

Claims 13-18, 40, 41, and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In re Wands (8 USPQ2d 1400 (CAFC 1988))

In the Examiner's opinion, the specification teaches that cells are stained using various procedures, as outlined on pages 18 to 19. From this, samples are processed according to the methods of pages 23 to 27, in which the color image is processed from RGB to HLS signals.

The instant claims, however, do not reflect such steps of cell staining or cell tagging such that one of skill in the art would know how to perform the method of isolating a cell sample, fix a cell sample and locate rare cell candidates to produce a color image. Without steps of labeling or staining, the generation of a color signal for processing is not possible and the claims are not enabled.

Further, the Examiner contends that the claims are drawn to fixing a sample comprising rare cells in cell aggregates (blobs) in a monolayer. However, the claims are allegedly not enabled for fixing a sample in cell aggregates into a monolayer. One of skill in the art would not know how to fix an aggregate such that a monolayer would be formed in order to effectively image a sample to find a rare cell without disassociating the aggregate in order to form a monolayer.

d) In the Examiner's opinion, the claims are not enabled for methods of rare cell image identification by color image manipulation as there are allegedly no cellular identification labels or stains to generate a color image for processing and identification of a rare cell.

e) It would have been well known in the art that increasing the sensitivity of microscopically detecting cellular characteristics requires staining or labeling. This is a more effective way than simply evaluating morphology alone. For example, Mesker et al. (Cytometry (1994) Vol. 17, pages 209-215 PTO From 1449 document) teaches the detection of rare cell events using image cytometry in which markers are used to stain cells of interest in different colors. Analysis of the cell images, obtained at different wavelengths, result in high contrast to specifically recognize the different markers. Therefore, in order to generate a color image, staining and markers must be used. The instant claims, however, are not enabled for the generation of a color image.

f) and g) The skill of those in the art of cytometry is high. However, absent steps of labeling or staining in the claims, one of skill in the art would not know how to generate or receive a color image signal.

h) The claims are broad because they are drawn to receiving a color image without the appropriate steps in which to generate the image from the cell sample.

Applicant's Response:

Applicant respectfully disagrees. On the contrary, the presently claimed process provides an automatic computerized microscopic vision system for digitally observing both stained and unstained or native cell colors. Applicant has amended the subject matter of

cancelled claim 44 in newly added claim 47, which is believed to overcome the various objections. One of ordinary skill would know that, e.g., fetal blood cells are very distinct from the maternal red blood cells in size, morphology and color, see paragraph [0054]. One of ordinary skill in blood pathology would easily differentiate by eye between a nucleated fetal blood cell candidate and an enucleated mature doughnut shaped mature or mother red blood cell. Therefore, contrary to the Examiner's contention, staining is not an absolute requirement for a first identification. In view of the sensitivity of the digital optics, staining with dyes or diagnostic tools is not requisite for low power selection of target rare cells [0048-0051]. Moreover, the refractile properties of cell blobs also aid in digitized imaging of the rare cells. As presently claimed the invention provides image analysis for both unstained or native images as well as stained or tagged cells. The removal of the alleged lack of enablement rejection under the above referenced statute is requested.

Rejections under 35 U.S.C. 112, second paragraph

The Examiner's Position

Claims 13-18, 40, 41, and 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the following reasons:

Claim 13 recites "wherein the step of producing a rare cell image mask". There is insufficient antecedent basis in the claim for this limitation. No such step is in newly added independent claim 44. Clarification is requested.

Claim 14 recites “and applying a thick filter enhancing the selected rare cell signal”. It is unclear if these are two separate steps or if the “applying a thick filter” is a step that “enhances the selected rare cell signal”. Clarification is requested.

Claim 17 recites “acquiring an image of the body fluid or tissue smear”. There is insufficient antecedent basis in the claim for “the. . . tissue smear”. Claim 44 recites only a tissue. Clarification is requested.

Claim 18 recites “the rare cell data set”. There is insufficient antecedent basis in the claim for “data set”. Clarification is requested.

Claim 40 recites “the digitized color image”. There is insufficient antecedent basis in the claim for this limitation, as no digitized image is present in claim 44. Clarification is requested.

Claim 44 recites “cell aggregates (blobs)”. It is unclear whether these are intended to be the same or if they are different. Are cell aggregates considered “blobs”? Clarification is requested.

Claim 44 recites “(blobs)” in step (i) and in step (iii) recites “said blob”. It is unclear if the blobs of step (i) are the same or different from the “blob” of step (iii), as one is singular and one is plural. Clarification is requested.

Claim 44 recites “said optical field”. There is insufficient antecedent basis in the claim for such a limitation as no “optical field” limitation preceded step (iii). Clarification is requested.

Claim 44, step (viii), recites “automatically locating by a selective tag dispensing system which is programmed to tag selectively said rare cell in situ to determine biological criteria comprising genomic variation, mutation, or chromosomal aberration”. The claim step is unclear, as it is grammatically incorrect. Is intended that the step “automatically locates. . . to determine”

or is it intended that the step “automatically locates” and the “tag” determines biological criteria. Clarification is requested.

Claim 45 recites “a sequence of computer directed steps to identify a rare cell image in accordance with claim 44”. It is unclear what steps are implemented by a computer that actually isolate a sample. How can a computer or a computer readable medium isolate a sample?

Clarification is requested.

Claim 46 recites “the computer-controlled method for rare cell image identification”. There is a lack of antecedent basis, as it is unclear what computer-controlled method is intended. Clarification is requested.

Claim 46 is unclear as to it is what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 46 is also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101.

Applicant's response:

Applicant respectfully traverses the Examiner's reasons for the rejection. On the contrary, the alleged deficiencies of claim 44 have been amended in replacement claim 47. All the objections of the Examiner are believed answered by the amendment of claim 44 in the form of replacement claim 47.

Claims 13, 14, 17, and 18 have been amended in accordance with the Examiner's comments.

The rejection of claim 46 is deemed moot in view of the cancellation of the claim.

Claim 40 is clearly derived from Claim 47, step (iv), of digitally receiving, i. e. digitized, color image signal.

In view of the amendment and remarks set forth above, Applicant respectfully asserts that the rejections of the pending claims 13-18, 40, 41, 45, and 47 under 35 USC 103 is deemed improper, and should be withdrawn, which favorable action is solicited.

CONCLUSIONS

An early notice of allowance in the next Office action is earnestly requested.

Respectfully submitted,

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